REMARKS/ARGUMENTS

Reconsideration of the present application, as amended, is respectfully requested.

A. STATUS OF THE CLAIMS

As result of the present amendment, claims 2, 4-10, 12, 14-19, 21, 27, and new claims 28-37 are presented in the case for continued prosecution.

Claim 1 has been cancelled without prejudice.

Claim 27 has been amended to include a polyalkylene oxide recited in original claim 13. Claim 27 has also been remove some Markush group elements from the definitions of the L_2 group. In addition, the claim has been amended to correct a typographical error found in "-$(CH_2)_r$-S-S-$(CH_2)_q$-Q'-" defined as the L_2 group. The (r') is missing. Support can be found, for example, in the counterpart L_3 group in cancelled claim 1 and on page 26, line 2 through page 27, line 6. Claim 27 has also been amended to remove the reference to the formula "(I)" to address objections raised in the Office Action.

Claim 2 has been amended to include a missing punctuation.

Claim 3 has been cancelled without prejudice.

Claim 7 has been amended to remove an informal punctuation.

Claim 9 has been amended to include a polyalkylene oxide in conformance with claim 27, as amended herein.

Claim 10 has been amended to remove the terms "each" and "independently" to address objections raised in the Office Action.

Claims 12 and 15 have been amended to remove some Markush group elements.

Claim 13 has been cancelled without prejudice.

Claim 14 has been amended to correct a typographical error with respect to "polyethylene glycol".

Claim 21 has been amended to recite "wherein".

New claims 28-36, drawn to a product prepared by a process, have been added to set forth what the Applicants believe to be their invention. Support can be found in the specification as filed. The definitions defined in the claims correspond to those of claims 2, 5-9, 14, 17-18 and 27.

New claim 37 has been added to recite embodiments. Support can be found, for

example, on page 39, line 29 through page 42, line 10.

Withdrawn claims 20 and 23-26 have been cancelled without prejudice.

Withdrawn claim 22 has been amended to correspond to claim 27, as amended herein.

No new matter has been added.

B. CLAIM OBJECTIONS

On page 2 of the Office Action, claims 10 and 27 are objected to because claim 10 recites "each" for the X_2 group although only one X_2 group is recited, and claim 27 recites formula (I) which reference has been already used in claim 1 for compounds with a different scope than that of claim 27.

In response, the informalities found in the claims have been corrected by removing the terms "each" and "independently" in claim 10, and the reference to "(I)" in claim 27. Claim 27 has also been amended to include the orientation of the formula corresponding to that as included in formula (I) in original claim 1. No new matter has been added.

Reconsideration and withdrawal of the objections is respectfully requested.

C. SUMMARY OF THE INVENTION

The claimed prodrug, as amended herein, is directed to a polymeric oligonucleotide conjugate. The claimed compound is a polymeric oligonucleotide delivery system in which an oligonucleotide modified with the C2-C10-containing L_2 pacer is conjugated to a polymer via a releasable linker. The claimed invention provides an oligonucleotide delivery system which is able to load higher amounts of oligonucleotides compared to prior art systems. In addition, the claimed invention eliminates needs for lipid-based carriers for the delivery of oligonucleotides. These features are advantageous in therapy employing oligonucleotides because prior art therapy required transfection agents which have toxicity, which is not desirable in application to humans. The claimed invention provides safe and superior means for oligonucleotide therapy.

D. DECLARATION UNDER RULE 132

Applicants respectfully request that the Examiner takes into consideration the Declaration under Rule 132. At the outset, the Examiner will note that the Declaration is unexecuted, however, the data contained therein was provided by the Declarant and the unexecuted Declaration has been forwarded to the Declarant for execution. Thus, in order to expedite prosecution in this application, it is respectfully requested that the Examiner consider the data as contained in the Declaration. The executed Declaration will be submitted as soon as it is received by the below-signed.

E. CLAIM REJECTIONS UNDER 35 USC 103

1. Summary of Rejection

On pages 3-7 of the Office Action, the Examiner has rejected the subject matter of all pending claims under 35 U.S.C. 103(a) as being allegedly unpatentable over Teng et al. (U.S. Patent No. 6,887,906) in view of Greenwald et al. (U.S. Patent No. 6,303,569) and Dandliker et al. (U.S. Patent No. 5,707,813).

The Examiner has alleged that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to produce the bcl-2 sequence of Teng in a polymeric prodrug form, as taught by Greenwald et al. The Examiner further alleged that it is obvious to use hexylamine linkers as a component of the polymeric prodrug according to Dandliker.

In addition, the Examiner took the position that Greenwald and Dandliker cure the deficiency of Teng.

Applicants respectfully traverse.

2. The Claimed Polymeric Oligonucleotide Prodrug is Not Obvious

As explained in detail below, Teng in combination of Greenwald and Dandliker proposed by the Examiner is not sufficient to render the claims, as amended herein, *prima facie* obvious pursuant to the principles of MPEP 2143.01 VI. The rejections rely upon an impermissible hindsight guided almost exclusively by the teachings of the instant application itself.

According to **MPEP 2143.01 VI,**

> If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious…The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.). (Emphasis added).

It is important to appreciate the elements and the principle of operation of Teng's system. Teng discloses *lipids-based* delivery systems for the delivery of nucleic acids. The delivery system includes a non-covalently linked lipid carrier. The lipid carriers help nucleic acids cross the cell membrane. Nucleic acids admixed with the lipid carriers are released from the carriers in the body.

Greenwald discloses a polymeric prodrug for the delivery of various biologically active agents. The system of Greenwald is based on a *polymeric* double prodrug. A target drug is covalently linked to a polymeric delivery system via a releasable linker.

The modification proposed by the Examiner would drastically change the elements and the principle of operation of primary reference Teng or Greenwald. According to Teng's delivery system, nucleic acids should be admixed with sufficient amounts of lipid carriers. Teng described that nucleic acids in prodrug form as an alternative to nucleic acids in native form can be employed in the Teng's lipids-based system.[1] As mentioned in Zhao's Declaration, one of ordinary skill in the art would not modify nucleic acids with a polymer to include the polymeric forms of nucleic acids in the lipid-based system of Teng. Nucleic acids in polymeric prodrug form are not desirable to Teng's system. The *bulky* size of the polymeric portion of Greenwald is disadvantageous to formulate complexes of lipids-based carriers and polymeric forms of nucleic acids. Accordingly, Teng uses nucleic acids in non-polymeric form to maintain the lipid-based delivery system. See Teng at column 17, lines 63-67, wherein SATE-modified oligonucleotides in non-polymeric prodrug form are disclosed. There is nothing in Teng to suggest use of polymeric forms

[1] Teng at column 17, line 17 through column 20, line 1 described various oligonucleotide alternatives. See the section entitled "5. Bioequvalents".

and as set forth in Zhao's Declaration, such a combination is not particularly useful given the bulkiness conveyed by the polymer portion. Additionally, the polymer taught in Greenwald is *hydrophilic*. This hydrophilic feature is not suitable for formulation of complexes with *hydrophobic* lipids-based carriers. See item 15 of the Declaration.

Teng and Greenwald, at best, teach different technologies for the delivery of nucleic acids. The combination of the references proposed by the Examiner would require a substantial change in the operating principle of Teng's delivery system. It is respectfully submitted that the proposed combination would hamper the operation of Teng's system substantially.

In addition, Applicants respectfully ask for clarification concerning the Examiner's remarks found in the paragraph bridging pages 6-7 of the Office Action.[2] The linker and spacer of Greenwald do not correspond to L_1 and L_2 groups of the formula in the claims, as proposed by the Examiner. Instead, the combined moiety of the aforementioned linker and spacer of Greenwald correspond to the L_1 group of the formula of the claims. The spacer designated as L_2 in Greenwald is not the L_2 group of the present application. Clarification in detail is provided at items 16-19 of the Declaration. Greenwald is silent with respect to the C2-C10 carbon-containing bifunctional spacer designated as the L_2 group of the claimed invention.

Dandliker relates to an oligonucloetide probe for *in vitro* assay. Dandliker discloses that the probe includes an oligonucleotide permanently linked to a fluorophore dye. The compounds of Dandliker do not release oligonucleotides. The bonding is permanently linked to the dye so that the compounds of Dandliker function as a reliable marker in *in vitro* assay. Nowhere does Dandliker teach release of the oligonucleotide

[2] The Examiner remarked: "These arguments are unpersuasive because contrary to applicants' assertions, Greenwald et al. do teach the claimed configuration of elements. As stated in the rejection, Greenwald et al. teach at columns 2-3 a prodrug comprising a polymer region designated as R_{11}, a linker comprising an aromatic group (which is equivalent to L_1 of the instant claims), a spacer designated as L_2 (which is equivalent to L_2 of the instant claims) and a drug component designated as B (which can be an oligonucleotide). Greenwald et al. further define L_2 at column 3 as spacers containing more than 2 carbons. Since Greenwald et al. explicitly teach polymeric prodrugs with the components found in the claims and further define L_2 to be a spacer group that comprises 2-10 carbons, those in the art are not left to try to prepare indeterminate linkage combinations of polymeric prodrugs and non-polymeric prodrugs, all that is needed to produce the claimed compounds is found in the cited references and could be combined with reasonable expectation of success to form the claimed compounds." Emphasis added.

which is called for a polymeric prodrug. See item 13 of the Declaration.

None of the references relied by the Examiner, taken alone or in combination, teaches or suggests the claimed invention including (1) a polymer; (2) a releasable linker; (3) a C2-C10-containing bifunctional spacer; and (4) an oligonucleotide.

Applicants respectfully submit that an **impermissible hindsight** relying almost exclusively on the guidance provided by the instant specification has been employed.

The claimed invention, as amended herein, is an unexpectedly superior oligonucleotide delivery system compared to prior art. The claimed invention is not a case which meets the obviousness inquiry that "a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" in *KSR Intl. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1735, 82 USPQ 2d 1385 (2007).

It is very important for polymeric oligonucleotide delivery systems to be able to load sufficient amounts of oligonucleotides in great yield and purity. The Declaration shows that *only about 7%* of nucleic acids conjugated to the prior art polymeric system of US Patent No. 6,180,095 (Exhibit **3** in the Declaration) which is similar to Greenwald. See item 24 of the Declaration.

On the other hand, *more than 30% and up to 90%* of the nucleic acids modified with the claimed L_2 spacer were reacted with polymers containing an L_1 group. According to the claimed invention, conjugation to the nucleic acids provided about four (4) times, at minimum, and up to 12.8 times of the polymeric prodrugs, compared to the prior art system. See items 25-29 in the Declaration.

In addition, the modified oligonucleotide successfully conjugated to a variety of polymers including different releasable linkers and/or activating groups. The oligonucleotide at either 3' or 5' position was attached to the spacer. Since the claimed invention includes different C2-C10-containing bifunctional spacers, artisans in the art can employ different releasable linkers and spacers, and use different activating groups, as desired to accommodate their needs. For example, the claimed polymeric oligonucleotide system can include different releasable linkers to modify release rate of oligonucleotides from the polymeric prodrugs.

According to the claimed invention, greater amounts of nucleic acids conjugated to various polymers, forming a *uniform linkage* between the releasable linker and the claimed

C2-C10-containing spacer and having a *uniform loading* of the oligonucleotide per prodrug due to the linkage of the L_1 and L_2 groups. These features are advantageous to prepare a uniform pharmaceutical formulation required for a reliable treatment regimen. Unlike the claimed invention, the prior art system would result in a mixture of products with different linkages and different loadings of oligonucleotides per prodrug because of the multiple functional groups on the oligonucleotides.

The unpredictability of a successful polymeric delivery system capable of loading high payloads and providing uniform products was confirmed by the Declaration. The Declaration also confirmed that the claimed invention is a superior system in loading higher amounts of nucleic acids which is necessary for a nucleic acids delivery system, compared to the prior art and providing prodrugs with uniform linkages and uniform loading of nucleic acids per prodrug.

The references cited by the Examiner provided no evidence that the linkage of the releasable L_1 linker and the C2-C10-containing L_2 spacer would provide the unexpected results, such as up to about 12.8 times in loading of nucleic acids as compared to prior art. The ordinary artisan would have had no reasonable expectation of success that polymeric systems would yield the unexpected results.

The claimed invention provides superior means for the delivery of oligonucleotides into the body compared to the prior art, and is not obvious over the references relied upon by the Examiner. As such, it is respectfully submitted that the Examiner has not made a *prima facie* case of obviousness. For all of the amendments and the reasons, reconsideration and withdrawal of the rejection is respectfully requested.

F. FEES

This response is being filed with an RCE and a petition for a three-month extension of time. Claim fees for the total twenty-six (26) claims, including three (3) independent claims, were paid initially. As a result of the amendments, the total twenty eight (28) claims, including three (3) independent claims, are provided. However, Applicant notes that one independent claim fee (claim 27) was not submitted in the previous response of July 2, 2008. The required fees are being submitted via credit card authorization. If it is determined that any further fees are due or any overpayment has been made, the Assistant

Commissioner is hereby authorized to debit or credit such sum to deposit account 02-2275.

Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

G. CONCLUSION

In view of the actions taken and arguments presented, it is respectfully submitted that each and every one of the matters raised by the Examiner have been addressed by the present amendment and that the present application is now in condition for allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

LUCAS & MERCANTI, LLP

By: /Michael N. Mercanti/
Michael N. Mercanti
Registration No. 33,966

Hyun Soon Cho
Recognition No. L0306

LUCAS & MERCANTI, LLP
475 Park Avenue South
New York, New York 10016
Phone: 212-661-8000
Fax: 212-661-8002